Clinical Nutrition 43 (2024) 268–283

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPEN Endorsed Recommendation

The science of micronutrients in clinical practice – Report on the ESPEN symposium☆

Mette M. Berger [a, *], Karin Amrein [b], Rocco Barazzoni [c], Laure Bindels [d], Irene Bretón [e], Philip C. Calder [f], Stefano Cappa [g], Cristina Cuerda [h], Patrizia D'Amelio [i], Angélique de Man [j], Nathalie M. Delzenne [k], Alastair Forbes [l], Laurence Genton [m], Adrian F. Gombart [n], Francisca Joly [o], Alessandro Laviano [p], Christophe Matthys [q], Pyi Pyi Phyo [r], Paula Ravasco [s], Mireille J. Serlie [t], Alan Shenkin [u], Nicole U. Stoffel [v, w], Dinesh Talwar [x], Arthur R.H. van Zanten [y]

[a] Lausanne University, Faculty of Biology & Medicine, 1005 Lausanne, Switzerland
[b] Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, 8036 Graz, Austria
[c] Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy
[d] Faculty of Pharmacy and Biomedical Sciences, Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium
[e] Nutrition Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[f] School of Human Development and Health, Faculty of Medicine, University of Southampton and NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton SO16 6YD, UK
[g] IUSS Cognitive Neuroscience (ICoN) Center, University School for Advanced Studies (IUSS-Pavia), 27100 Pavia, Italy
[h] Departamento de Medicina, Universidad Complutense de Madrid, Nutrition Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[i] Service de gériatrie et réadaptation gériatrique, Département de Médecine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[j] Department of Intensive Care Medicine, Research VUMC Intensive Care, Amsterdam Cardiovascular Science, Amsterdam Infection and Immunity Institute, Amsterdam, the Netherlands
[k] Metabolism and Nutrition Research Group, Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium
[l] Institute of Clinical Medicine, University of Tartu, Tartu, Estonia
[m] Clinical Nutrition Unit, Department of Endocrinology, Geneva University Hospitals, Geneva, Switzerland
[n] Linus Pauling Institute, Department of Biochemistry and Biophysics, Oregon State University, Corvallis, OR 97331, USA
[o] Beaujon Hospital, APHP, Clichy, University of Paris VII, France
[p] Department of Translational and Precision Medicine, University La Sapienza, Rome, Italy
[q] Human Nutrition, KU Leuven, Leuven, Belgium
[r] WHO European Office for the Prevention and Control of Noncommunicable Diseases, WHO Regional Office for Europe, Copenhagen, Denmark
[s] Coordinator of the Curricular Units Diabetes, Obesity and Lifestyle, Digestion and Defence, University of Lisbon - Católica Medical School, Lisbon, Portugal
[t] Department of Endocrinology and Metabolism, Amsterdam University Medical Centers, Amsterdam, the Netherlands
[u] Institute of Aging and Chronic Disease, University of Liverpool, Liverpool, UK
[v] Laboratory of Human Nutrition, Department of Health Sciences and Technology, ETH Zurich, Switzerland
[w] MRC Human Immunology Unit, MRC Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK
[x] Department of Biochemistry, Glasgow Royal Infirmary, Glasgow, UK
[y] Gelderse Vallei Hospital, Ede and Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, the Netherlands

☆ **WHO Disclaimer**: WHO authors alone are responsible for the views expressed in this article, and they do not necessarily represent the views, decisions, or policies of the WHO or institutions with which they are affiliated.

* Corresponding author. Lausanne University, Faculty of Biology & Medicine, 1011 Lausanne, Switzerland.
E-mail addresses: mette.berger@unil.ch (M.M. Berger), karin.amrein@medunigraz.at (K. Amrein), barazzon@units.it (R. Barazzoni), laure.bindels@uclouvain.be (L. Bindels), irenebreton@gmail.com (I. Bretón), P.C.Calder@soton.ac.uk (P.C. Calder), stefano.cappa@iusspavia.it (S. Cappa), cuerda.cristina@gmail.com (C. Cuerda), Patrizia.DAmelio@chuv.ch (P. D'Amelio), ame.deman@amsterdamumc.nl (A. de Man), nathalie.delzenne@uclouvain.be (N.M. Delzenne), alastair.forbes@ut.ee (A. Forbes), Laurence.Genton@hcuge.ch (L. Genton), adrian.gombart@oregonstate.edu (A.F. Gombart), Francisca.joly@aphp.fr (F. Joly), alessandro.laviano@uniroma1.it (A. Laviano), christophe.matthys@uzleuven.be (C. Matthys), phyop@who.int (P.P. Phyo), pravasco@ucp.pt (P. Ravasco), m.j.selie@amsterdamumc.nl (M.J. Serlie), shenkin@liverpool.ac.uk (A. Shenkin), nicole.stoffel@hest.ethz.ch (N.U. Stoffel), dinesh.talwar@ggc.scot.nhs.uk (D. Talwar), zantena@zgv.nl (A.R.H. van Zanten).

https://doi.org/10.1016/j.clnu.2023.12.006

ARTICLE INFO

Article history:
Received 5 November 2023
Accepted 7 December 2023

Keywords:
Trace element
Vitamin
Deficiency
Epidemiology
Immunity
Inflammation

SUMMARY

Background & aims: The European Society for Clinical Nutrition and Metabolism published its first clinical guidelines for use of micronutrients (MNs) in 2022. A two-day web symposium was organized in November 2022 discussing how to apply the guidelines in clinical practice. The present paper reports the main findings of this symposium.
Methods: Current evidence was discussed, the first day being devoted to clarifying the biology underlying the guidelines, especially regarding the definition of deficiency, the impact of inflammation, and the roles in antioxidant defences and immunity. The second day focused on clinical situations with high prevalence of MN depletion and deficiency.
Results: The importance of the determination of MN status in patients at risk and diagnosis of deficiencies is still insufficiently perceived, considering the essential role of MNs in immune and antioxidant defences. Epidemiological data show that deficiencies of several MNs (iron, iodine, vitamin D) are a global problem that affects human health and well-being including immune responses such as to vaccination. Clinical conditions frequently associated with MN deficiencies were discussed including cancer, obesity with impact of bariatric surgery, diseases of the gastrointestinal tract, critical illness, and aging. In all these conditions, MN deficiency is associated with worsening of outcomes. The recurrent problem of shortage of MN products, but also lack of individual MN-products is a worldwide problem.
Conclusion: Despite important progress in epidemiology and clinical nutrition, numerous gaps in practice persist. MN depletion and deficiency are frequently insufficiently searched for in clinical conditions, leading to inadequate treatment. The symposium concluded that more research and continued education are required to improve patient outcome.

1. Introduction

In November 2022, The European Society for Clinical Nutrition and Metabolism (ESPEN) organised a web symposium aiming at clarifying the application of its recent micronutrient (MN) guidelines [1] in clinical practice. During the first day, the symposium focused on the fundamental physiology of MNs, while the second day was oriented towards their clinical application in a selection of conditions including cancer, obesity with impact of bariatric surgery, diseases of the gastrointestinal tract, critical illness, and aging: The present papers summarise the different lectures and the discussion from the symposium.

1.1. Aims of the ESPEN micronutrient guideline

Micronutrients i.e., trace elements and vitamins, are essential components of nutrition, but precise knowledge regarding their use in clinical settings is not widespread. To assist clinicians in the identification of specific MN needs and administration as part of medical nutrition therapy (MNT), the ESPEN MN guidelines were published in 2022 [1]. They aimed at providing practical information about the assessment of MN status and the prescription of the different MNs, while attracting attention to specific MN needs in patients receiving enteral nutrition (EN) or parenteral nutrition (PN). The guidelines also aimed at contextualizing the population needs formulated as recommended dietary allowances (RDAs) or the more recent dietary reference intakes (DRIs) and needs in disease.

An important part of the MN guidelines focused on language standardization (Table 1).

The first three general recommendations of the guidelines apply to all MNs:

1. Adequate amounts of all essential trace elements and vitamins shall be supplied to all patients receiving medical nutrition from the beginning of the period of nutritional support.
2. Micronutrient supplements shall be provided orally or enterally if this can be done safely and effectively.
3. C-reactive protein (CRP) should be determined at the same time as any micronutrient analysis (alternatives to CRP may be Interleukin-6 or α-acid glycoprotein, but not hs-CRP)

As the PICO (Patient, Intervention, Comparison, Outcome) question strategy could not be applied to all MNs, the most common pathologies seen in patients at high risk of MN deficiencies were listed while providing a systematic approach to the individual MNs. For each of them, the relevant section of the guidelines summarized the main functions, the needs, the biomarkers with recommended analytical methods, the impact of inflammation, the consequences of deficiency, toxicity, and recommendations about measurement and doses used for standard nutrition and treatment of deficiency.

1.2. Status assessment

To orient therapy, MN status assessment may be required as a baseline assessment upon initiation of MNT or after a long period of inadequate intake [1]. Such assessment requires a combination of history, examination, and laboratory tests. Initially, it also requires an assessment of recent intake and probable losses, and careful examination for traditional signs of MN deficiency.

Biological alterations affecting metabolism may result from MN deficiencies and may become apparent before the classical signs of deficiency are seen. Examples are increasing blood homocysteine may reflect folate deficiency, methylmalonic acid that of vitamin B12, the excretion of organic acids biotin deficiency, or for molybdenum deficiency urinary sulphite, blood xanthine or hypoxanthine. Glucose intolerance may be a manifestation of chromium deficiency.

Blood testing has numerous pre-analytic caveats such as correct sampling (e.g. lack of residual infusion or oral intake, lack of contamination from needle or tube), or correct timing (e.g. there is a peak of plasma zinc and iron in the early morning) [2]. Using validated analytical methods of analysis is essential. For trace elements inductively coupled plasma mass spectrometry (ICP-MS) is now the most used and accurate method, with the use of an internationally agreed reference material. For vitamins there is a greater variety in methods, many using high performance liquid chromatography (HPLC) or mass spectrometry – however

Table 1
The language defining micronutrient status and prescription.

Status	ESPEN definition and comment
Optimal status	Intake meets losses; tissue and metabolic functions are optimized (although the latter can be difficult to assess)
Adequate	Intake meets losses; plasma concentrations are normal in the absence of inflammation
Depletion	Intake does not meet losses or plasma concentrations are low; no physical or metabolic signs of inadequacy are observable
Deficiency	Intake does not meet losses or plasma concentrations are low; physical or metabolic signs of inadequacy are present
Toxicity	History of inadequate high intakes; blood levels are in the toxic range; presence of clinical signs or symptoms of toxicity
Prescription	
Complement	Delivery of MNs to cover basal needs, e.g. to complete enteral feeds, such as during insufficient EN [2,3]
Repletion	Doses aiming to restore the normal status and where the deficit is known. Sometimes called supplementation when the doses required to restore status are very high
Supplementation	Term used when the aim is to deliver higher than standard doses (i.e. superior to DRI or PN recommendation). The term does not include pharmaco-nutrition.

interlaboratory comparisons are more difficult because of the lack of an international standard. All laboratories should establish their own appropriate and validated reference ranges.

Nevertheless, plasma (or serum) concentrations of MNs only reflect extracellular fluid which does not necessarily correlate with intracellular concentration or functionality. There are alternatives to plasma measurements, such as red blood cells (RBCs) for vitamins B1, B2, B6, and folate (vitamin B9) and for manganese, selenium and zinc: these methods are more reliable than plasma. For vitamin C, leukocytes may be used, while urine collection is used for iodine and fluoride. Enzyme activities can be useful biomarkers of status, as they reflect functions such as plasma or RBC glutathione peroxidase for selenium, RBC transketolase for vitamin B1, or transaminase for vitamin B6.

For a few MNs, the binding and storage proteins may guide status assessment: this is the case for iron with transferrin, the soluble receptor of transferrin, ferritin and hepcidin. Copper status assessment is supported by plasma caeruloplasmin, while selenium adequacy is defined by the level of selenoprotein P. Holotranscobalamin reflects Vitamin B12 status.

Each centre should define its own approach using the available resources to obtain the most accurate assessment of the combination of history, examination, and laboratory testing.

1.3. Impact of inflammation

Blood level determination assumes that blood reflects tissue stores and status, which is not necessarily true. Blood concentrations may be sufficient to indicate frank deficiency or toxicity, but sensitivity and specificity of blood levels can be problematic in disease. For some MNs, plasma levels fall only when tissue stores are significantly depleted as for vitamin A. In addition, most MN functions occur within cells. Plasma concentrations are therefore indirect and relatively insensitive indicators of status which is poorly reflected by extra-cellular fluid levels.

Furthermore, many factors can influence blood levels, inflammation being preponderant. Part of the response to disease, injury or infection is the acute phase response (APR), which causes many carrier proteins to decline in plasma, these being called negative APR proteins. The effect is to lower the plasma levels of many MNs. Thus, the APR may affect plasma levels independently of tissue status, as the plasma levels of several MNs fall due to the redistribution of their binding proteins and uptake by the tissues, making plasma levels unreliable indicators of their status.

In acute inflammation, resulting from even minor physiological events [3], plasma MN levels can fall transiently by as much as 50 % and tend to normalize without dietary interventions as inflammation begins to resolve (Fig. 1). The inflammation-related alterations start within hours [4].

This decrease is mainly due to inflammation-driven redistribution, and increased cellular uptake (liver, immune cells) and excretion; eventual loss can also contribute. It is not possible to quantify the relative contribution of these different mechanisms on the basis of plasma MN concentrations.

In chronic inflammation, triggers and causes are multifactorial: dietary factors, consumption factors and losses will combine, complicating the assessment. Alternative biomarkers, not or less affected by inflammation, will assist in the determination of some

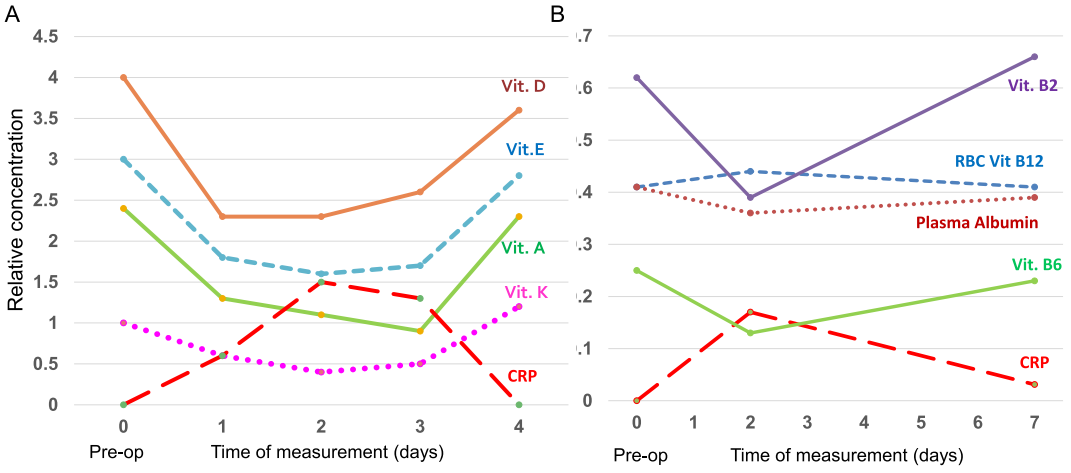

Fig. 1. Status of fat-soluble vitamins and CRP (A) and water-soluble vitamins, albumin and CRP (B) in the days after knee arthroplasty. CRP concentrations peaks at day 2, accompanied by a transient fall in the plasma level of fat-soluble vitamins (up to 60 %). Similarly, for some of the water-soluble vitamins (e.g. B2 and B6), there is a transient fall of about 50 % in plasma concentrations at day 2 when the CRP concentration peaks and then a tendency to normalise as inflammation resolves.

MNs [2]. Such are available for copper, iron, selenium, and B vitamins (see above). In some cases, plasma MN levels can be corrected to their carrier process (protein, lipoproteins) such as with the vitamin E/cholesterol ratio, vitamin K/triglyceride ratio and zinc/albumin ratio. Therefore, accurate and reliable MN status determinations require a systematic structured approach.

2. Immunity and oxidative stress

2.1. Oxidative stress and inflammation

Inflammation is part of the host defence response; it is initiated by exposure to triggers (infection, damaged tissue etc.) that activate the inflammatory response that is manifested by cellular movement, cellular activation, and the production of a multitude of chemical mediators. Cellular activation, cell phenotype and chemical mediators can all be assessed as a means to diagnose and monitor inflammation [5]. In this regard, total white cell count, acute phase proteins such as CRP and cytokines such as interleukin-6 (IL-6) are commonly measured. Inflammation should be self-limiting (self-resolving); resolution is an active process [6]. Loss of resolution results in persistent inflammation that can become damaging to the host, causing significant pathology (Fig. 2). Chronic high-grade inflammation is causally linked to overt inflammatory and autoimmune conditions such as rheumatoid arthritis, inflammatory bowel disease and asthma as well as to sepsis [7]. Chronic low-grade inflammation is a risk factor for common non-communicable conditions such as cardiovascular disease, type-2 diabetes, and cognitive decline and is linked to loss of muscle and bone mass and to many cancers [5,7]. Chronic low-grade inflammation increases with age [8] and with obesity [9]. There is a bidirectional interaction between oxidative stress and inflammation in that oxidative stress can induce inflammation, for example by activating the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway, while inflammation induces oxidative stress as part of host defence.

Therefore, at least in theory, antioxidants can reduce inflammation. This is evident in preclinical cell culture and animal models. There is also some evidence from human trials and systematic reviews of randomized controlled trials (RCTs) find that vitamins C and E decrease circulating CRP and inflammatory cytokine concentrations [10–13]. Such effects are dependent upon dose, duration and type of patient studied. Such studies usually measure inflammatory markers in blood collected before and after a period of supplementation; participants are usually in a resting state when the blood is collected. However controlled challenges can be used to assess the effect of an intervention on the dynamics of the inflammatory response; such challenges include the administration of endotoxin, use of UV irradiation, or the use of exercise, a high fat meal or a high sugar meal (or drink) with serial blood collection in the period afterwards. The combination of high dose vitamin E and vitamin C was found to blunt the rise in the concentrations of inflammatory cytokines and adhesion molecules that was seen in the blood of diabetics following consumption of high fat and high carbohydrate meals [14]. Although dose is important, there is insufficient information about the dose–response relationship between antioxidant vitamins in humans and the inflammatory response, and also about effects across the range of possible target groups.

2.2. Immunity & infectious diseases

MNs play key roles in every step of the immune response [15]. Viral, bacterial and parasitic diseases are all worsened by MN deficiencies due to multiple adverse effects on immune function. MN deficiencies are widespread and compromise not only the immune system (amongst others), but they hinder child growth and development. MN deficiency is a worldwide issue, as shown by a survey including 22 countries demonstrating that globally 372 million preschool-aged children and 1·2 billion (1·0–1·4) non-pregnant women of reproductive age (15–49 years) had one or more MN deficiencies [16]. MNs with low status include vitamin D, vitamin B12, folate, vitamin A, iron, and zinc, and these are often combined. Such deficiency is associated with exacerbation of existing illness, especially infectious diseases, but also impaired mental and physical development.

Among the MNs, selenium, iron, zinc and vitamins A, C and D are in the first line of defence, as the body's physical barriers, i.e. the skin and respiratory epithelium, are totally dependent on these MNs for integrity [15]. Therefore it is not surprising that MN supplements, particularly vitamins C and D, reduce the risk of respiratory infections as shown in various meta-analyses, and may even shorten an active respiratory tract infection when used as therapy [17].

To ensure an optimal immune response against viral infections requires sufficient intake of MNs [18]. Already in 2001, Beck showed in a mouse model [19] that increased oxidative stress of a host due to selenium deficiency can lead to changes in the genome of some viruses suggesting that host nutritional status may be an important mechanism for the development of emerging viral variants with new pathogenic properties.

Evidence in favour of MN supplements reducing the risk of acute infection does exist, with different levels of evidence (Table 2) supporting the rationale of adequate MN status. The odds of tuberculosis (TB) increase with deficiencies in vitamin A and zinc, which are frequent in several low- and middle-oncome countries

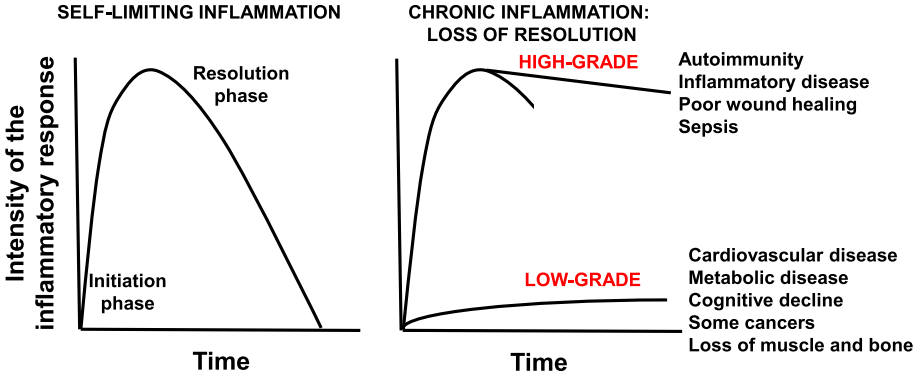

Fig. 2. Differences between a self-limiting inflammation and a chronic high- or low-grade non-resolving inflammation.

Table 2
Effects of supplements on reducing the risk of acute infections.

Micronutrient	Disease impact	Level of evidence
Vitamin A	Increased risk of measles and diarrhea in children	Low-to-moderate quality
Vitamin C	Decreased cold incidence (>50 %)	High quality
	Decreased pneumonia in adults and children	Low-to-moderate quality
	Lower risk of UTI in pregnancy (100 mg)	Low-to-moderate quality
Vitamin D	Decreased risk of RTIs (daily supplementation optimal)	5 meta-analyses, most high quality
Zinc	Decreased risk of ear infections in children, RTI, pneumonia, diarrhea	High quality
Multi-vitamin and mineral supplement	Fewer Infections in young adults,	Low-to-moderate quality
	Fewer days of infection in older adults	
	Most apparent in undernourished >6 months	

Abbreviations: UTI = urinary tract infection, RTI = respiratory tract infection.

[20]. TB can be present alone or as coinfection in HIV patients. A RCT conducted in Botswana showed that the administration of selenium alone or in combination with multivitamins to these patients significantly lowered the risk of developing incident TB [17]. In critical illness also, MN deficiencies favour infections that are prevented/treated by repletion of copper, selenium and zinc as in burns, with reduction of nosocomial pneumonia [21].

For therapeutic interventions, the evidence is weaker, except for vitamin C regarding severity and duration of common cold symptoms [17,18]. Increased intake of vitamin C during the onset of illness may also provide added benefit [22]. There are also some benefits with vitamin D treatment in TB, influenza and upper respiratory tract infections (RTIs) [18]. Zinc acetate doses >75 mg/day have been shown to efficiently shorten duration of common cold in adults and children if administered within 24 h of symptom onset [23]. Zinc is efficient both in prevention and treatment of diarrhea [24].

Among the vitamins, vitamin D is particularly important for innate immune function. When macrophages (and epithelial barrier cells) encounter pathogens, they synthesize the active form calcitriol 1,25$(OH)_2$D and upregulate vitamin-targeted genes like the cathelicidin antimicrobial peptide (CAMP/hCAP-18 and LL37) which are important for the innate immune response to infection. Low vitamin D status may be a modifiable risk factor for COVID-19. A recent systematic review and meta-analysis that included 72 observational studies showed vitamin D deficiency/insufficiency increased the odds of developing COVID-19 (odds ratio [OR] 1.46; $P < 0.0001$ %), severe disease (OR 1.90; $P < 0.0001$) and death (OR 2.07; $P = 0.003$) [25]. Subsequently, another meta-analysis which included 10 RCTs, and 16 observational studies, showed vitamin D supplementation may be associated with lower intubation rate and shorter length of hospital stay, although it was not associated with any mortality reduction [19]. Vitamin C and zinc did not produce such beneficial effects [26].

The overall body of evidence emphasizes that improving MN status through diet and complementing diet with supplements represents a strategy to support the immune system and to reduce risk and severity of infectious diseases. Rather than the use of MNs like drugs, we should ensure adequate MN intake to optimize immune function and in the case of vitamin C and zinc, consider increasing intake during the appearance of symptoms.

2.3. Vaccination in children

Vaccinating against paediatric infectious diseases saves 4–5 million lives every year, but these vaccines do not always work well in the context of malnutrition and MN deficiencies. Therefore vaccines often underperform in low- and middle-income countries and leave 15–20 % of fully vaccinated children unprotected, contributing to 1.5 million deaths every year from vaccine-preventable diseases [27].

Recent studies suggest that iron deficiency not only causes anemia but may also weaken the immune system. Activated immune cells need high amounts of iron to produce antibodies in response to vaccines. Iron deficient immune cells proliferate poorly and have decreased antibody production [28].

In a recent birth cohort study, 573 Kenyan infants were followed for two years. Infants received polio, DTP (diphtheria, pertussis, polio), haemophilus and pneumococcal vaccines at 6, 10 and 14 weeks of age. Iron status was measured at time of vaccination and vaccine response was measured at 6 and 18 months. Iron deficiency and low haemoglobin was the strongest predictor of poor response to polio, diphtheria and pertussis vaccines [27]. Infants with anemia had five times the risk of measles vaccine failure and twice the risk of diphtheria vaccine failure.

In a secondary analysis of a previous RCT it was investigated whether iron given at the time of measles vaccination improves the vaccine response. 127 iron deficient Kenyan infants received 12 mg iron or no iron from 7 to 11 months of age. All infants received the measles vaccine at age 9 months. Infants receiving iron at the time of measles vaccination had a better primary vaccine response, with higher anti-measles antibodies, higher seroconversion rates and also greater anti-measles IgG avidity [27].

3. Some specific MN issues

3.1. Updating MN needs

EURRECA (EURopean micronutrient RECommendations Aligned) is a European network created several years ago to address the lack of a standard framework to determine MN recommendations, causing confusion among consumers, producers and policy makers. Having a standard framework for MN recommendation development represents the intakes judged sufficient to meet requirements of most healthy individuals within a population group [29].

The steps encompass defining the nutrition-related health problem, defining the process, establishing robust methods, collating sources of evidence, and summarizing and integrating the evidence into recommendations. How to define the endpoints in the determinations of the requirements was the first question that considered public health importance, new evidence, and priority populations, resulting in 28 MNs being identified for 6 different population groups. The second question addressed the issue of translating requirements to recommendations, considering clinical outcomes and based on dose response curves.

The high prevalence of chronic disease and the relatively higher MN needs to prevent them was integrated in the process aiming at chronic disease risk reduction. These do not replace the DRI categories which have been designed for the global population independent of disease, but change how evidence on chronic disease risk is assessed and used to modulate the DRI process. A causal

relationship was needed for consideration. An example of the intake response is observed with fibres which decrease risk of disease and rarely have side effects: the balance between optimal value and deficiency is essential to consider when establishing DRI [30]. Different examples were discussed (omega-3 PUFA, iron) showing the importance of addressing the right population, generic polymorphisms and inflammation. Questions are still open such as defining core outcome measures.

3.2. Iodine deficiency in Europe

WHO recommends sodium intakes of less than 2 g/day (less than 5 g of salt) while recommending iodine intakes of 150 μg/day for adults and adolescents (120 μg/day in children) increasing to 250 μg/day for pregnant and lactating women. Monitoring iodine intake is realised using spot urine samples, as well as monitoring iodine content of foods. Data from 2007 showed that iodine intake was insufficient in 11 European countries, adequate in 20, and excessive in one country. The Iodine Global Network published data in 2021 (some rather old) showing insufficient intakes in several European countries (Fig. 3): iodine deficiency remains a significant health and socio-economic problem. The costs in terms of productivity are likely to be significant but are yet unknown.

Salt fortification is the preferred strategy to deliver iodine, salt being a good vehicle for iodine, and the technology being efficient and inexpensive. According to Iodine global network (IGN) data updated in 2016, use of iodized salt is voluntary in 17 countries and mandatory in 26 countries, while 7 countries do not have legislation on iodine requirements. Accelerating new data collection on iodine status is required. The WHO European Regional Office in collaboration with IGN with the support of Kiwanis International is developing an updated report on iodine deficiency in Europe ("A solution at our doorstep (Part A & B)") in order to address the key issues such as iodine status data in school-age children, women of reproductive age and pregnant women; an evidence-based evaluation of the consequences of mild and moderate iodine deficiency in Europe to better define the magnitude of the problem; alternative sustainable strategies for monitoring iodine status; data on the iodized salt distribution and the use of iodized salt in processed food and alternatives strategies to tackle iodine deficiency integrating the regulatory heterogeneity.

Salt reduction policies and salt iodization policies are compatible. Both require food industry engagement and similar surveillance modalities. Continual monitoring to ensure consistent delivery of iodine and to allow for adjustments in the amount of iodine added to salt is necessary in response to decreased population sodium intake. The WHO is also working on updating the global MN database including iodine and reviewing current guidance around indicators for the assessment of iodine status.

3.3. Iron in clinical nutrition

Iron has multiple functions beyond oxygen transport. Particularly it is involved in immune function as previously discussed. Iron deficiency is a global public health issue, affecting most women, but also children, adolescents, and older adults. Iron deficiency is a factor complicating the clinical management of over 50 % of heart failure patients [32].

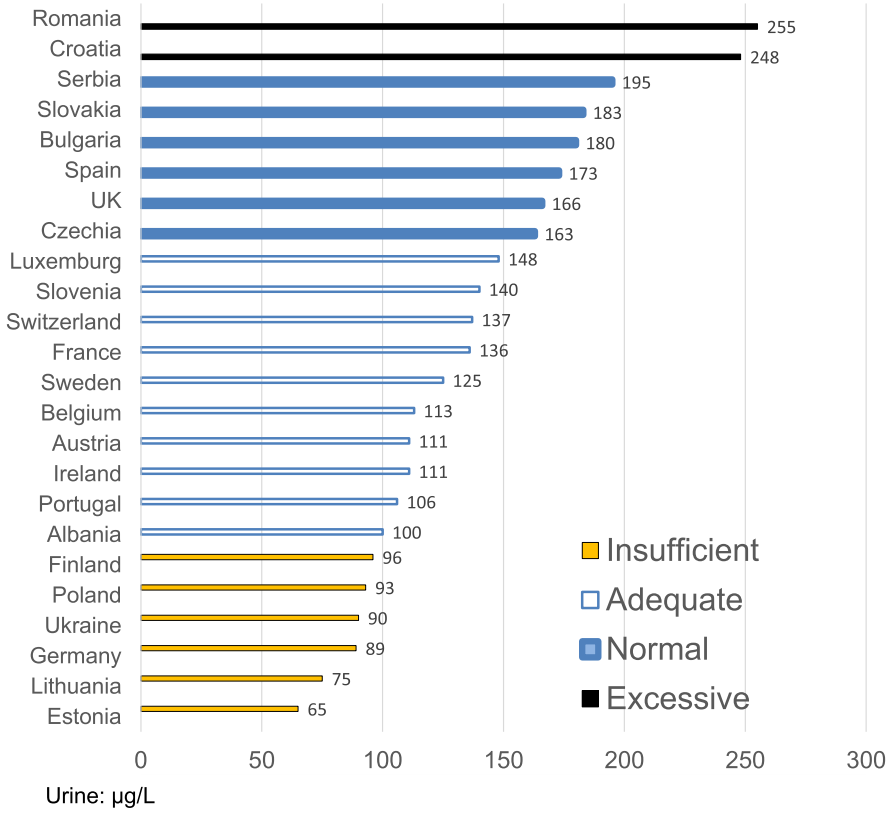

Fig. 3. Selected national iodine intakes in the European region, with median urine concentrations (μg/L) in the general population based on those in school age children. WHO cut-offs for children >6 yr: I < 50 μg/l moderate to severe deficiency, 50–99 μg/l insufficient, 100–199 μg/l adequate, 200–299 μg/l above needs, >300 μg/l excessive. Adapted from WHO 2021 data [31].

A retrospective study from the Mayo clinic including 185 patients on home PN, showed that 32.4 % were iron deficient [33]: development of deficiency was a question of time, and was most rapid in patients with intestinal fistulae and bowel obstruction. As multi-trace element products containing iron were not available, the clinicians had to add iron dextran as maintenance therapy.

The ESPEN guideline [1] strongly recommends assessing status and ensuring that iron is delivered at nutritional doses during both EN and PN. This has been the case in Europe for over 30 years. This insistence is because in many non-European countries, the multi-trace element products available for PN do not contain iron, leading to the inevitable development of anemia in patients dependent on PN [33], that compromises outcome. The guideline also recommends treating iron deficiency when diagnosed with the recent formulations of iron supplements as their use after the peak of inflammation has proven safe in randomised trials with significantly higher haemoglobin levels [34] and even decreased mortality [35]. When treating a patient, iron status is threatened by disease, low intakes and poor absorption and is particularly difficult to assess in the presence of inflammation. Ferritin, a widely used marker, is misleading because it increases sharply with inflammation, being an acute phase response protein.

Optimal iron deficiency diagnosis shall include a combination of tests: plasma iron, transferrin, transferrin saturation, ferritin, CRP, soluble transferrin receptor (sTfR), hepcidin, and evaluation of red blood cell (RBC) morphology [1]. Hepcidin, while still not widely available, has been shown to be a reliable biomarker: sTfR is also only modestly affected by inflammation.

3.4. MN needs in clinical nutrition

The ESPEN MN recommendations for enteral nutrition (EN) were formulated for a delivery of 1500 kcal/day [1], which, based on an isocaloric formulation of 1 kcal/ml, provides 1500 ml/day (EN is often prescribed in ml). This concept aimed at covering minimal requirements while delivering clinically realistic amounts of feeds. International surveys indicate that, while this amount of energy is the most commonly prescribed target, feed delivery is generally low, with around 1000 kcal/day often being delivered [36]. Since all the MNs are incorporated in the EN formula, the amount of each MN supplied depends on the volume of feed that is provided. Table 3 provides the amounts using a commonly used 1 kcal/ml EN product as an example: the table compares the amounts of 8 selected MNs according to the delivery of 3 levels of energy compared to the DRI and to the European Council directive [37].

In patients receiving less than 1500 kcal/day, an additional enteral or intravenous provision of MNs may be considered, especially if there is a recent history of poor intake [38].

The PN-products face a different problem: they are conceived as one-size-fits-all. Therefore, monitoring at intervals is highly recommended, particularly in home PN patients who depend on these preparations for prolonged periods and may not receive adequate amounts of MNs.

3.5. MN product availability and shortage

With the publication of guidelines [1], MN administration should be considered part of standard care in patients dependent on PN. However, not all countries benefit from a complete availability of multi-MN products providing the full range of essential MNs [39]. Single intravenous trace element (copper, chromium, selenium, zinc) and vitamin products are non-existent in most countries, preventing individualised corrections of deficiencies.

Historically, the multi-trace element and multi-vitamin products were developed for adult patients on long-term PN. With the development during the 2 last decades of the use of multi-chamber bags which contain no MNs, the administration falls short of individual adaptation. The multi-MN products should ideally be administered separately, as they cannot be premixed for stability reasons. Further, to facilitate administration, clinical teams tend to inject the MN products into these bags, often under questionable sterility conditions, with associated risks.

Further, shortage of MN products for intravenous use, especially vitamin preparations, has become a recurrent problem on all continents, exacerbated by the COVID-19 pandemic. An unpublished ESPEN survey conducted in 2021 showed that 32 % of 52 intestinal failure centres had experienced shortages for durations that varied between 7 and over 90 days. This raised questions about the criteria determining prioritization of patients, definition of monitoring frequency, modality of individual MNs, administration, and reimbursement of non-IV preparations. ASPEN, having been confronted with both vitamin [40] and trace element [41] shortages, and BAPEN, with similar experiences [42], had generated recommendations for their members. The ESPEN dedicated home artificial nutrition (HAN) and micronutrient (MN) special interest groups (SIGs) decided to update and adapt the recommendations for Europe, to provide general principles to assist professionals to deal with the problem [43] (Table 4).

During shortage, the available MNs should be reserved for some categories of patients highly or totally dependent on MNs e.g. neonates, pediatric patients receiving PN and intolerant to oral/enteral MNs, patients with inherited metabolic disorders, patients with IF unable to absorb any MNs, patients on long-term PN, patients on home PN unable to absorb any oral or enteral MNs, IF with high GI losses, patients at high risk of refeeding syndrome, and patients on PN requiring critical care.

Table 3
Amounts of MNs received by patients depending on the quantity of energy delivery using product "XYZ", which is provided as 500 ml bags. For thiamine, the DRI is covered with the lowest 900 kcal prescription and even the highest dose does not exceed European Council (EC) safety limits [37]. But for the low intake, DRI needs are not covered with this solution for vitamins C, D, and E and iron. In no case are the EC upper limits exceeded.

MN	XYZ content	Prescribed:			DRI	EC directive [37]
	500 ml @ 1 kcal/ml	900 kcal	1500 kcal	1800 kcal		
Vit B1 mg	0.65	1.2	2.0	2.3	1.1–1.2	0.9–7.5
Vit C mg	33.5	60.3	100.5	120.6	75–90	34–330
Vit D µg	5	9.0	15.0	18.0	15–20	7.5–37.5
Vit E mg	6.5	11.7	19.5	23.4	15	7.5–45
Copper mg	0.665	1.2	2.0	2.4	0.9	0.9–7.5
Iron mg	6.5	11.7	19.5	23.4	30	7.5–30
Selenium µg	33.5	60.3	100.5	120.6	55	37.5–150
Zinc mg	6	10.8	18.0	21.6	8–11	7.5–22.5

Table 4
General principles to apply in case of MN product shortage.

Reserve IV multivitamins or multi trace elements for some priority indications and temporarily use oral/enteral route for multivitamin or multi trace element administration if this can be done in a safe and effective manner.
Assess each patient regarding the indication for PN and provide vitamins and trace elements via the sublingual, oral or enteral route when possible and deemed to be safe (excluding patients with malabsorption syndromes). The vitamin profile should be reviewed, and missing components supplemented, if available.
All the measures which "compensate the shortage" should be considered as "degraded alternatives" and therefore patients require increased monitoring of micronutrient status.
As soon as shortage resolves, the current recommendations of IV multivitamin and trace element prescription should be applied.

The type of intestinal failure, and the duration of the required PN are important determinants of the "rescue" strategy. And in case of shortage, monitoring becomes even more important than usual [2]: it should be more frequent.

4. Micronutrients and disease

4.1. Cancer

4.1.1. Antioxidants - friends or foes in cancer?

Increased oxidative stress contributes to tumor initiation and progression. Several MNs counteract oxidative stress, and therefore patients with cancer frequently use them, even during chemotherapy. More than 80 % of patients with breast cancer take multivitamin supplements, vitamin C, D and E being the more prevalent [44]. However, chemotherapy may be based on induced oxidative stress to kill cancer cells, and thus MNs with antioxidant properties may reduce the clinical efficacy of the treatment. A study including 1134 patients with breast cancer, showed that the use of antioxidants/MNs before and during treatment does not influence survival, whereas iron or vitamin B12 supplementation negatively influences outcome with poorer disease-free survival ($P < 0.01$) and overall survival ($P < 0.01$) [45]. The findings of this study suggest caution for patients when considering the use of MNs and urge them to report their use to the attending oncologist. Regular use of MN supplements may also reveal a philosophical approach to therapy. In this regard, breast cancer patients consuming dietary supplements tend to consult and start chemotherapy later, which may be detrimental [46]. Animal studies appear to suggest a benefit when combining immune checkpoint inhibitors with ascorbic acid, but clinical confirmation is still lacking [47]. In summary, no general recommendations can be delivered at this stage, and medical advice should be always sought before initiating or continuing MN supplementation.

Nevertheless, a poor diet present before and during cancer therapy can result in malnutrition and deficiencies that are deleterious: therefore while cautioning against high doses of any MN, it is recommended to use multi-MN products with doses close to the DRIs [48,49].

4.1.2. Impact of antitumor therapy on MN status

Malnutrition is frequent in cancer and is the principal, though not only, cause of MN deficiencies (Fig. 4) [50]. In breast and colorectal cancers, low vitamin D seems associated with worse survival and poor prognosis. Other associations have been suggested with deficient vitamin D status, i.e. higher severity of radiation-induced acute proctitis, osseous effectiveness of bisphosphonates, and high risk of melanoma.

L-carnitine deficiency is associated with cancer risk and poor outcome: 80 % of patients with advanced disease are carnitine deficient due to inadequate diet and competition with cytostatics (anthracyclines for the transporter OCTN2, necessary to transport L-carnitine into cells, disruption of L-carnitine biosynthesis by anthracyclines, increased renal excretion by cisplatin/ifosfamide).

Vitamin C deficiency is found particularly in patients with advanced disease; patients with lower vitamin C seem to have increased inflammatory activity (higher CRP), poor nutritional condition, and shorter survival time. Zinc has also been explored: a scoping review including 34 articles showed an association between low zinc and dysgeusia and dysosmia in lung cancer patients, and tailored zinc supplementation has been suggested [51].

Depending on cancer nature, site, and stage, 30%–90 % of patients have an inadequate diet. Malnutrition affects intake and availability of MNs. Evidence shows that patients who consume

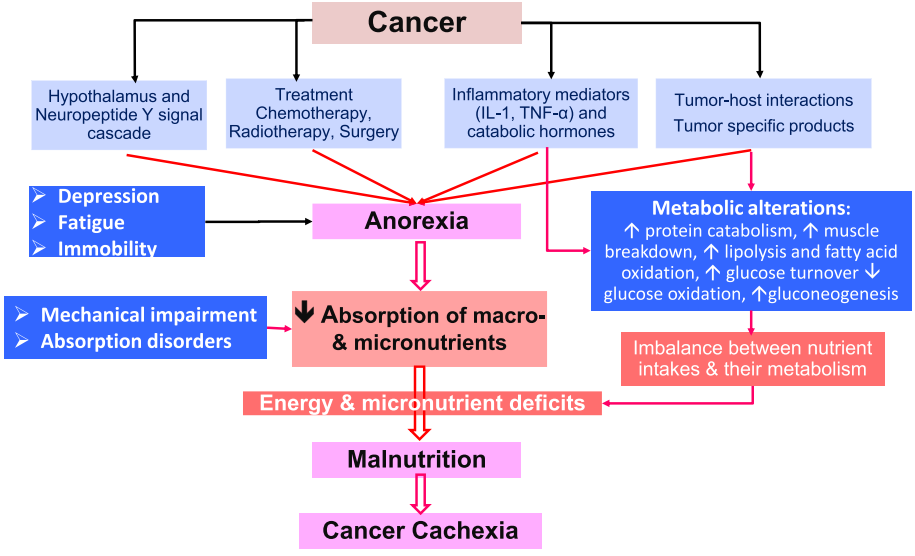

Fig. 4. Causes of malnutrition and micronutrients deficiencies in cancer. Adapted from Gröber et al. [50].

<60 % daily energy requirements for 7–10 days have inadequate supply of MNs and losses and requirements may be increased by the effects of chemo or radiotherapy (vomiting, diarrhea, dysgeusia) and inflammatory processes.

At the start of treatment, MNs with limited storage capacity (vitamins B1, C, folate, K) are particularly critical. In patients with surgery and/or bleeding, zinc deficiency is frequent. Optimal supply of MNs (RDA amounts) should be assured, in addition to an adequate supply of energy substrates (proteins, fats, carbohydrates). Cancer- and/or treatment-induced MN deficiency impacts the disease course and effectiveness of cytoreductive measures, increasing risk of complications. Diagnosis of deficiency and optimal supply of MNs should be monitored.

4.1.3. Cancer cachexia and MNs

The prevalence of cachexia differs with cancer type, is a determinant of prognosis and may cause cancer treatment interruption [52,53]. The gut microbiota directly influences host immunity and metabolism: in animals, a synbiotic intervention restored intestinal homeostasis and improved outcome by reducing cancer proliferation and cachexia [54].

Treatment of cachexia is multifactorial and includes physical activity, pharmacological interventions, and nutritional therapy: the latter is currently poorly defined with studies including heterogenous populations and different MNs [55].

Vitamin D has been investigated more in depth as it exerts biological actions on myogenic precursor proliferation and differentiation, impinging on muscle regeneration: deficiency has been shown to cause abnormalities in skeletal muscle and muscle wasting. In cancer, a retrospective study [56] showed 47 % of patients were vitamin D deficient. An encouraging retrospective study in breast cancer patients showed that the patients who were supplemented with vitamin D during chemotherapy had a longer disease-free survival and a tendency to higher BMI [57]. However, data are still insufficient to generate a firm recommendation, the more so that the optimal biomarker and vitamin D form are still unsettled.

4.2. Diseases of the GI tract

4.2.1. MN absorption and needs in intestinal failure

Intestinal failure (IF) is defined as a reduction of gut function below the minimum necessary for absorption of nutrients, and results in intravenous supplementation being required. The diseased population is very heterogeneous [58].

In short-term type I intestinal failure, vitamin provision is of critical importance, while issues with trace elements are rare. In longer-term IF, adequate vitamin replenishment remains crucial, particularly with vitamin D, but the problems with correct management of trace elements increase, seen both as deficiency and as toxicity. There are fewer problems in the patients who have less dependence on PN.

While acute IF occurs with increasing frequency, chronic IF is a rare disease [58]. Diseases leading to chronic IF include Crohn's disease, mesenteric ischemia, surgical complications, chronic pseudo-obstruction, and radiation enteritis. Survival rate of these patients when on PN is good, for example 80 % at 5 years.

Weaning off PN depends on the remaining length and function of the bowel. Food intake in these patients is highly variable, as is absorptive capacity and transit time, all factors that affect MN status. Absorption of MNs is either through passive transport or specific transporters and most MNs are absorbed in the proximal gut (duodenum and jejunum).

Assessment of MN status is challenging as it is often compromised by the presence of systemic inflammation (see earlier). The treatment needs to be personalized as the deficiencies depend on the intestinal segments that are affected by disease. Patients on PN are usually supplemented with intravenous MNs and therefore timing of MN assessment, i.e. time of blood drawing, is variable affecting the laboratory result: a few hours should probably separate end of MN infusion from blood sampling. Preliminary data show that in 114 patients with chronic IF on PN, the prevalence of high concentrations of the trace elements zinc and selenium is between 20 and 30 % while below reference range concentrations of zinc were present in less than 10 % of the population. In 300 patients with chronic IF and on PN, deficiencies of vitamins A and D were most prevalent while above reference range concentrations of vitamin B6 were present in 45 % of patients.

Among vitamins, B12 is especially vulnerable in those with short bowel, but being well-known is easy to handle; most other vitamins are usually adequately catered for by commercial fixed-ratio vials. In lipid-free PN, vitamin K deficiency can become a problem as it is absent from some vials: in that case, vitamin K should be added as complement. Biotin deficiency can also be a problem because it is not present in all products. There are no problems with vitamin excess, nor any major problems with vitamin premixed bags for home PN. Among minerals, magnesium requires special attention.

For trace elements, standard commercial mixtures are less satisfactory with generally too little selenium, and too much manganese. The limited availability of individual trace elements makes ideal management difficult or impossible.

As an example, Abdalian et al. [59] showed that, despite excess in prescription compared to recommendations (Table 5), blood zinc level was normal, manganese was high, and selenium was low. The manganese excess is a problem as it can result in a Parkinson-like pathology. Copper excess, or more rarely deficiency, can present with hematological problems or neurological symptoms.

Iron deficiency is common in IF, although its treatment is theoretically straightforward with modern single-agent iron infusions, given that the amount of iron that can be added to PN without stability problems is very low. However, continued management is challenging as iron deficient patients have increased gastrointestinal iron absorption, and in patients on supplementary PN it is therefore difficult to estimate the amount needed parenterally for maintenance without risk of iron overload.

Copper toxicity is a concern in long-term care. A Canadian HPN survey indicated that excessive amounts were regularly being

Table 5
Comparison of average daily prescribed MNs in 135 Canadian patients on home PN compared to ASPEN and ESPEN recommendations (adapted from Abdalian et al. [59]).

Trace element	Prescribed mean ± SD mg (μmol)	ASPEN 2002 guideline [60] mg (μmol)	ESPEN 2022 guideline [1] mg	Provision versus guidelines
Copper	0.64 ± 0.35 (10.1 ± 5.6)	0.3–0.5 (4.73–7.88)	0.3–0.5	Excess
Chromium	11 ± 5 (0.21 ± 0.10)	10–15 (0.19–0.29)	10–15	Adequate
Selenium	78 ± 45 (0.99 ± 0.57)	20–60 (0.25–0.76)	60–100	Adequate
Manganese	452 ± 184 (8.2 ± 3.3)	60–100 (1.09–1.82)	55	Excess
Zinc	8.6 ± 5.5 (130.9 ± 84.2)	2.5–5.0 (38.8–76.5)	3–5	Excess
Iodine	77 ± 42 (0.61 ± 0.33)	Not defined	130	Insufficient

administered [59], and an American study indicated excess serum copper in a quarter of patients [61]. Although typical European prescribing in HPN does not often appear to cause copper toxicity [62], there have been considerable concerns in patients with cholestasis of any cause, and especially in patients with intestinal failure-associated liver disease (previously attributed only to PN) [63]. The liver copper is pathologically elevated in such patients: it is possible that copper has a modest casual role in the condition itself.

Together these problems form a strong rationale for regular MN status monitoring in patients dependent on HPN.

4.2.2. Microbiome – MN synthesis

The gut microbiome secretes numerous metabolites including B group vitamins and vitamin K2 [64]. The capacity of the human intestine to absorb the B vitamins produced by the microbiome is still uncertain: animal data seem to indicate that it occurs. In humans, gut microbiome studies indicate this might be the case as urinary excretion is higher than intake [65], but not all B vitamins are absorbed (like B2). Recent studies unravelled the role of microbial production of vitamins in the management of host metabolism, namely in the context of obesity [66]. The microbiome synthesis of vitamins may also contribute to intestinal immunity.

Severe obesity has been shown to be associated with an absolute deficiency in bacterial biotin producers and transporters, whose abundances correlate with host metabolic and inflammatory phenotypes: there are suboptimal circulating biotin levels in severe obesity and altered expression of biotin-associated genes in human adipose tissue [67]. Strategies combining biotin and prebiotic supplementation might be integrated as future treatment options.

Oral intake of vitamins and other MNs can also affect the development of specific micro-organisms and thus MNs play a role in determining the gut ecology. There is cross-feeding between gut bacteria, some being prototrophs (produce vitamins) and other autotrophs (depend on vitamins produced by other bacteria). Furthermore, the microbiome may influence the absorption of minerals and trace elements, especially increasing that of iron and zinc at the colonic level. The involvement of individual microbiome characteristics in MN status appears a complex but interesting and important facet to study in the future.

4.3. Obesity and bariatric surgery

4.3.1. MN status in patients living with obesity

MN deficiencies are frequent in patients living with obesity. This has led the WHO to emphasize the “double burden of malnutrition” with MN deficiencies associated with macronutrient-energy excess. The level of evidence varies for different MNs, but as a notable example, vitamin D deficiency has repeatedly been shown in obesity as confirmed by comprehensive meta-analyses [68]. Still different MN profiles are assessed and described in different studies, with heterogeneity possibly partly depending on age, sex, comorbidities, and body composition as well as fat distribution. The most frequent cause of deficiency is considered to be low MN intake due to poor diet quality: vitamin D and E intakes may be most strikingly reduced, but vitamins A, B12, folate and zinc are also reported to be affected [69]. The additional question of potential higher MN requirements in obesity is still unresolved but may be an issue related to the higher body mass.

The consequences of MN deficiencies have been described especially regarding vitamin D, which may favour increased inflammation, loss of insulin sensitivity, loss of muscle mass and of bone density, leading to a higher prevalence of diabetes mellitus, sarcopenia, and osteoporosis. Iron deficiency and anemia have also been reported to be associated with complications. During the COVID-19 pandemic, numerous studies reported associations between low vitamin D levels, obesity, and severe forms of the disease [45,70].

For the reasons summarized above, MN status should be assessed in those patients seeking nutrition therapy, particularly in those exposed to low energy-diets or with planned bariatric surgery that may favour or worsen MN deficiencies. Doses of MNs may need to be adapted to BMI as shown by Sadat-Ali et al. for vitamin D: the standard fixed 2000 IU/d dose did not correct deficiency, whereas the higher (125 IU/kg/m^2) BMI adapted dose did [71]. The DRIs are likely to underestimate the MN needs of such patients and further research is needed to develop optimal treatment strategies.

4.3.2. MNs after bariatric surgery

With the increasing obesity pandemic, the number of bariatric procedures has increased worldwide to over 700,000 per year. Sleeve gastrectomy is the most frequently performed; Roux-en-Y gastric bypass and other malabsorptive procedures, such as on-anastomosis gastric bypass, bilio-pancreatic diversion or SADI-S are associated with the most striking alterations of MN status.

The risk factors for MN deficiency include pre-operative deficiency, low intake (food intolerance, taste alteration, eating disorder, depression, poor socio-economic status), low adherence to supplementation and malabsorption, due to the surgical technique itself or to complications (bacterial overgrowth, SIBO (Small Intestinal Bacterial Overgrowth)) (Table 6). It is important to be aware of these deficits as MN deficiency, particularly zinc and iron, can worsen the status by inducing anorexia, taste disturbances and malabsorption. Therefore, MN supplementation needs to be adapted to the patient's clinical condition and surgical procedure. Patient adherence needs to be monitored as it is highly variable and influenced by numerous factors including economic factors such as the cost of multi-MN treatment, and health care related factors such as annual medical visits [72].

Some MN deficiencies result in high-risk of severe complications. Thiamine deficiency can occur in patients with low dietary intake and nausea/vomiting and has been described with all bariatric surgery techniques. Neurological manifestations, ranging from confusion to peripheral neuropathy, may have dramatic consequences and require prompt therapy. Neurological sequelae may occur despite treatment. Deficiencies of other MNs, such as niacin, pyridoxine, riboflavin, ascorbic acid, and vitamins B12, A and E, as well as copper, can also lead to neurological disturbances after bariatric surgery [73,74].

Particular attention should be given to pregnant women, as deficiencies also have consequences for fetal development and risk of miscarriage and other complications: this is particularly true for folic acid and risk of neural tube defects [75]. Iron, vitamin D and

Table 6
Risk factors for micronutrient deficiency after bariatric surgery.

- Micronutrient deficiency prior to surgery
  - Iron, zinc, vitamin D, folate
  - Pre-surgical evaluation of nutritional status is needed
- Decreased intake
  - Food intolerance, taste alteration, eating pattern (e.g. vegans)
- Malabsorption
  - Surgical technique, complications (SIBO, fistula, etc.)
- Low adherence to supplementation
  - Post-operative complaints, cost, inappropriate medication for swallowing difficulty
- Other clinical conditions
  - GI diseases, any other acute or chronic disease
  - Alcoholism, depression, eating disorders
  - Pregnancy

zinc deficiencies are frequent and particularly relevant during pregnancy [76]. The doses of MNs required after bariatric surgery during pregnancy are higher than those of other patients [77].

4.4. Critical care

4.4.1. Vitamins in sepsis

Sepsis is a potentially deadly disease. Hypovitaminosis is frequent and MNs are candidates as co-adjuvant therapy because they have numerous sites of action on the immune system. While blood levels of most MNs are decreased in sepsis, there is little information about their optimum level and how this relates to tissue levels. Edema and inflammation that causes redistribution complicate the assessment of status.

Thiamine and ascorbic acid (AA) levels are often low to very low in sepsis and potential supplement candidates due to their functions [78]: causes for the low levels are numerous [79] (Fig. 5). Recent studies show that around 70 % of critically ill patients had hypovitaminosis C (plasma concentration <23 μmol/l) and about 30 % had vitamin C depletion/deficiency (plasma concentration <11 μmol/l): these percentages were even higher in patients with sepsis (88 % and 38 %, respectively) [79]. The prevalence of thiamine depletion/deficiency in critically ill patients is about 20 %, and may increase up to 70 % during ICU stay, being associated with an increase in mortality of up to 50 % [79].

Both vitamins have important antioxidant functions: thiamine is essential for energy production, and AA is an immunomodulator and essential for synthesis of catecholamines and endothelial stability [79]. After the HAT (hydrocortisone, ascorbic acid, thiamine) trial many studies were conducted, without repeating the same success. The recent LOVIT trial showed more persistent organ dysfunction and deaths in the vitamin C group [80]. Despite this trial (and including it) a meta-analysis including 18 RCTs, showed a significant improvement of the delta SOFA ($p = 0.001$ with IV vitamin C [81]. For the moment, the guidelines maintain the use of repletion doses but not of very high doses [1].

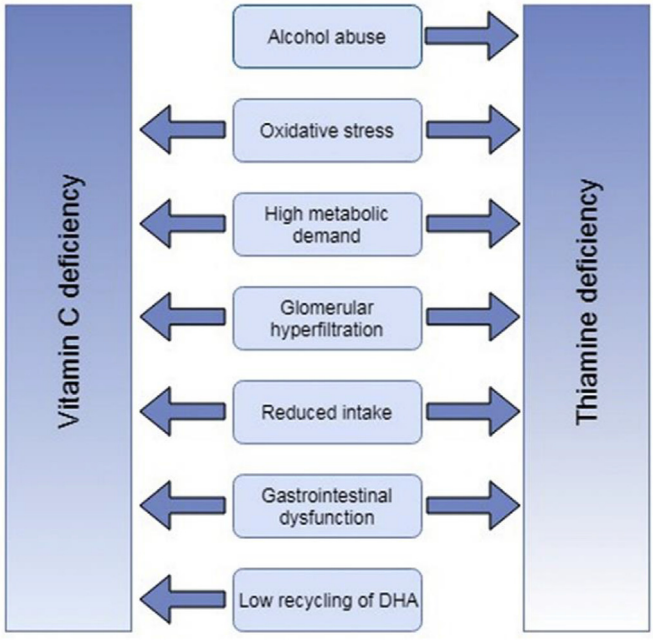

Fig. 5. Causes of vitamin C and thiamine deficiencies in critical illness. Reproduced with permission from [79]. Abbreviation use: DHA, dehydroascorbic acid.

Vitamin A blood levels are decreased in 65–81 % of the patients with sepsis. A trial tested 100,000 IU given intramuscularly for 7 days: the 28-day mortality rates were non-significantly higher in the vitamin A group (34 % vs 28 %) [82]. The recommended upper limit remains at 1500 ug/day [1]. Vitamin E is also generally low in patients with sepsis. In the absence of positive intervention evidence, only repletion doses are recommended.

4.4.2. Selenium

Selenium was first known for its toxicity, but in the 1990s it was recognized as an essential MN. Selenium is unevenly distributed worldwide with selenium-rich and selenium-deficient areas. Endemic Keshan disease in China drew attention to the importance of selenium in cardiac function [83] . The disease was caused by a combination of a coxsackie B3 infection and selenium deficiency, the latter increasing the virulence of the virus by lack of antioxidant defence. Selenoproteins have multiple functions including essential antioxidant function via different glutathione peroxidases (GPXs), redox signalling, thyroid hormones, protein folding, immunity, transport, and storage [84]. Most of these functions are heavily involved in heart function.

Selenium has a narrow therapeutic window, with increasing mortality with selenium levels below 100 μg/l and exceeding 150 μg/l [85]. Blood selenium is strongly impacted by inflammation: with CRP >40 mg/l, abnormal selenium levels are observed, which makes the simultaneous determination of biomarkers such as plasma GPX or selenoprotein P necessary for more precise assessment of selenium status [2].

Initial promising selenium supplementation trial results in critical illness showed reduced mortality that seemed confirmed by a meta-analysis [86]. The initial positive results were not confirmed by a German multicentre trial [87] and the REDOXS study [88], but different high and very-high doses were used. The latest meta-analysis distinguished between high doses (1000 μg) which were associated with prolonged ICU stay, and lower doses (500 μg) which were associated with reduced renal failure, as in the initial studies [89]. The difference may be related to a preexisting or acute depletion that justified correcting it as in major burns. Indeed in major burns, where acute depletion develops due to large exudative losses, doses of 300–500 μg have consistently been shown to exert positive effects [90].

The ESPEN guidelines insist on ensuring at least minimum amounts of selenium are provided in case of plasma values < 0.4 μmol/l in patients with elevated inflammation [1]: they also insist on delivering the full combination of essential MNs to all patients receiving PN.

4.4.3. Vitamin D

Vitamin D deficiency is a frequent worldwide problem affecting about 70 % of ICU patients and 40 % of the general population. It is associated with excess morbidity and mortality. This is related to the numerous functions of this prohormone [91,92]. A Cochrane review including 95,276 study participants showed that vitamin D supplementation was associated with a 6 % mortality reduction [93]: 150 people treated over five years were required (NNT) to prevent one additional death. Vitamin D supplementation also reduces acute respiratory tract infections [94], the effect being greatest in vitamin D deficient subjects. Emerging data also suggest a beneficial effect for oral vitamin D in reducing the progression to diabetes in subjects with prediabetes as shown in a meta-analysis of 3 high quality trials [95].

The use of single ultra-high bolus doses, although attractive, has been shown to be ineffective in rickets and other conditions [96]. The reason is that a single bolus dose induces long-term expression of the catabolic enzyme 24-hydroxylase and fibroblast growth

factor 23 (FGF23), both of which have vitamin D inactivating effects [97].

A 2022 meta-analysis on vitamin D3 in the ICU found that vitamin D may reduce mortality and that the parenteral route may confer greater benefits [98]. The ongoing VITDALIZE trial delivers a bolus of 540,000 UI followed by 4,000 IU/day of vitamin D3 in critically ill patients [99]. Current recommendations are to determine blood levels in case of suspected deficiency, and to deliver at least 2,000 IU per day, but not to deliver high single doses [1].

4.4.4. Refeeding syndrome (RFS)

This syndrome occurs during the reintroduction of feeding after a period of starvation or fasting. It is characterized by electrolyte and glucose metabolism abnormalities, particularly insulin resistance, putting patients at risk of thiamine deficiency.

Upon reintroduction of feeding, increasing blood glucose levels trigger insulin secretion, which leads to the movement of phosphorus, magnesium, and potassium into cells. This can result in various complex clinical signs and symptoms that are challenging to distinguish from other critical illness manifestations [100].

A prospective observational study among 337 patients, including 124 individuals with hypophosphatemia upon initiation of feeding, underscored the importance of phosphate monitoring. Interestingly, baseline characteristics did not significantly differ between those who developed hypophosphatemia, except for a minor and clinically non-relevant reduction in potassium and magnesium levels upon admission, which was observed in patients who developed RFS [101].

Doig et al. showed that in ICU patients with a drop of phosphate to below 0.65 mmol/l upon feeding initiation, energy restriction up to maximum of 500 kcal for 48 h improved survival rates [102]. This finding was corroborated by Olthof et al. [101]. Moreover, non-nutritional energy sources such as propofol, citrate, and glucose can also induce RFS, further emphasizing the importance of phosphate monitoring even when no nutrition is provided [101].

Considering the risks associated with RFS, a strategy to administer feeding progressively over the first few days is recommended [34]. After energy restriction, energy intake should be increased stepwise to the target, ideally measured by indirect calorimetry as per ESPEN-ICU guidelines [103] (Fig. 6).

Additionally, thiamine supplementation should be considered for patients with RFS, even though a recent RCT did not demonstrate significant clinical benefits of vitamin B1 supplementation in ICU patients [104].

RFS is not rare, with approximately one-third of long-stay critically ill patients experiencing it [32,36]. Given its prevalence, phosphate monitoring remains the primary means of detecting RFS in the ICU. Managing RFS in critically ill patients requires a multifaceted approach that involves careful phosphate monitoring and gradual feeding progression. The importance of early detection and tailored management strategies cannot be overstated, as they can significantly impact patient outcomes.

4.4.5. Micronutrients and physical activity

The information on the link between MNs and physical activity is scarce. Human studies evaluated the potential ergogenic effect of MNs on physical performance in athletes but not in normally active people or patients with disease. MNs directly involved in physical activity in muscle are vitamins B, C and E with trace elements copper, iron and zinc and the electrolyte magnesium (Fig. 7).

In athletes, as in other subjects, MN depletion occurs especially during energy restriction, extreme weight loss practices, elimination of one or more food groups, and globally poor diets. Iron, vitamin D and antioxidant vitamins are key MNs in athletes and have been associated, for instance, with muscle function, oxidative stress, and physical performance.

This raises the question of whether MN supplementation improves physical fitness. In a systematic review, iron supplementation in endurance sports has been shown to increase VO_2 max [106]. Vitamin D supplementation in athletes seemed not to be effective, with no improvement of muscle strength or power [107]:

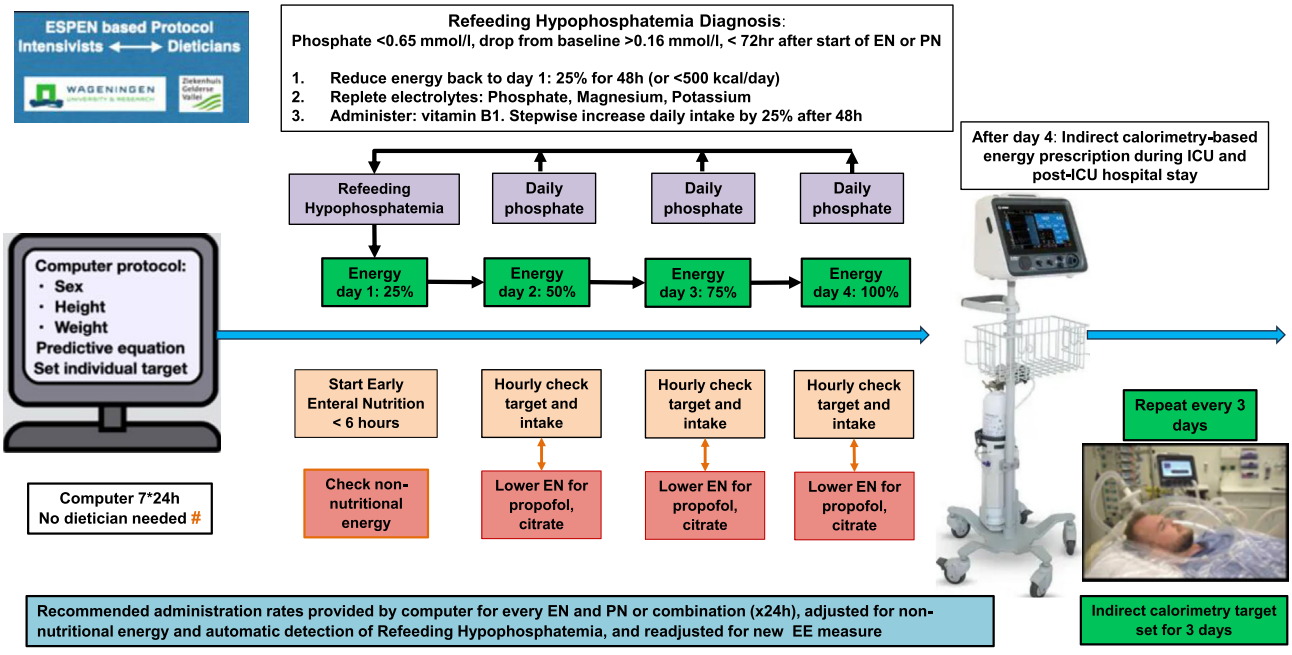

Fig. 6. Refeeding hypophosphatemia protocol for the ICU with gradual progression of energy intake and with daily phosphate monitoring. Example of the adaptation of the ESPEN guidelines to the Wageningen University hospital. # indicates that in a computerized ICU, the protocol enables handling the phosphate issue, sparing the dieticians for specialised tasks.

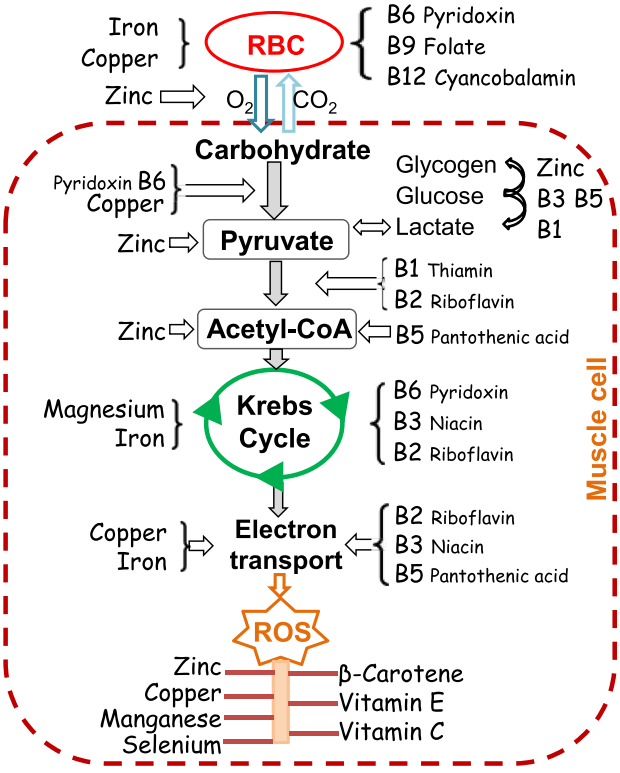

Fig. 7. Sites of action of the different MNs within the muscle. Abbreviations: RBC, red blood cell; ROS, reactive oxygen species. Adapted from Thomas et al. [105].

there is uncertainty about existence of an optimal vitamin D level, as the normal values are derived from osteoporosis studies. Finally, antioxidant supplementation might even decrease physical fitness in untrained individuals [108].

The only indications that are actually recognized in physically active people are iron and vitamin D for treatment of depletion, while administration of antioxidants is controversial [105]: food recording is important as athletes may have unbalanced diets with poor calcium, iron, selenium, and vitamin C and D intakes.

4.5. Geriatric requirements

4.5.1. MNs in sarcopenia and frailty

Healthy aging is of paramount importance in the face of increased life expectancy, and balanced nutrition positively affects healthy ageing. Healthy aging is opposed to frail aging; frailty is a multi-component syndrome associated with poor health outcomes and loss of independence. Age-related chronic diseases significantly contribute to frail aging, among these sarcopenia plays a fundamental role. The prevalence of sarcopenia varies between different studies reaching up to 29 % in community based older adults. Sarcopenia has characteristic features and significantly differs from healthy muscle aging [109]. Mitochondrial function is significantly altered in sarcopenia and nutritional intervention may rescue this as well as the clinical phenotype of sarcopenia. Several nutritional interventions have been used in sarcopenia; in particular protein at 1.2–1.5 g/kg day is effective in increasing muscle mass, though not muscle strength, in older adults [110]. More specific interventions using branched chain amino acids (BCAAs) administered to malnourished older adults show significant benefits on muscle strength, mass and performance; moreover this intervention is able to rescue impaired mitochondrial activity, reducing oxidative stress and increasing ATP production [111].

Data linking antioxidant MNs with sarcopenia are sparse. In a large prospective cohort with a 12-year follow-up, higher intakes of total carotenoids, lycopene, and lutein + zeaxanthin were associated with increased muscle strength, and all antioxidants except for vitamin C were associated with faster gait speed [112]. Nutritional supplementation with vitamin D combined with whey protein or BCAAs is effective in improving muscle strength regardless of the addition of physical exercise [113].

Although the optimal treatment strategy for older frail and sarcopenic patients is still not clear, the treatment of these patients must include protein and/or BCAAs supplementation associated with Vitamin D and physical exercise; the role for MN supplementation is not yet established.

4.5.2. MNs and cognitive impairement

Alzheimer's disease (AD) is the most epidemiologically relevant cause of cognitive decline in the elderly population. The current model of AD is dynamic, based on the concept of a pathological process evolving over decades, with a long asymptomatic stage, followed by the onset of progressive memory decline (Mild Cognitive Impairment), subsequently leading to dementia of increasing severity. There is now ample evidence supporting the effectiveness of modifying the risk factors associated with cognitive decline as an important prevention tool in AD. Nutrition is one of these factors, as indicated by several meta-analyses of dietary intervention studies supporting a key role for the Mediterranean diet in lowering risk [114].

Several MNs have been investigated for a potential protective role. These include B vitamins (folate, B6, B12), trace elements (copper, iron, zinc) and antioxidants (vitamin A, lutein, lycopene, zeaxanthin, cryptoxanthin, carotene, vitamins C and E) and also long chain fatty acids (docosahexaenoic acid). Neuroimaging studies of cortical thickness, an excellent marker of brain health have reported a positive association with the consumption of several dietary factors including vegetables, alpha-linolenic acid, beta-carotene and vitamin C [115]. Detailed information about the role of MNs remains however limited. In a recent study of 140 frail patients, nutritional status (assessed by the MNA-SF) was shown to be related to cognitive health, but no relation could be found with any individual MN [116].

5. Conclusion

The science of MNs has progressed during the last 2 decades. However, despite this progress, numerous gaps persist, especially regarding diagnosis of MN deficiencies in clinical situations, leading to insufficient treatment. The above clinical situations emphasize the importance of monitoring the MN status. Research and continued education about MNs are required to improve patient outcome. The recent ESPEN guideline [1] should be followed.

Conflict of interest

The authors declare no conflict of interest. There was no external funding.

References

[1] Berger MM, Shenkin A, Schweinlin A, Amrein K, Augsburger M, Biesalski HK, et al. ESPEN micronutrient guideline. Clin Nutr 2022;41:1357–424.
[2] Berger MM, Talwar D, Shenkin A. Pitfalls in the Interpretation of blood tests used to assess and monitor micronutrient nutritional status. Nutr Clin Pract 2023;38:36–69.
[3] Maguire D, Catchpole A, Sheerins O, Talwar D, Burns A, Blyth M, et al. The relation between acute changes in the systemic inflammatory response and circulating thiamine and magnesium concentrations after elective knee arthroplasty. Sci Rep 2021;11:11271.

[4] McMillan DC, Maguire D, Talwar D. Relationship between nutritional status and the systemic inflammatory response: micronutrients. Proc Nutr Soc 2019;78:56–67.
[5] Calder PC, Ahluwalia N, Albers R, Bosco N, Bourdet-Sicard R, Haller D, et al. A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. Br J Nutr 2013;109(Suppl 1):S1–34.
[6] Barnig C, Bezema T, Calder PC, Charloux A, Frossard N, Garssen J, et al. Activation of resolution pathways to prevent and fight chronic inflammation: lessons from asthma and inflammatory bowel disease. Front Immunol 2019;10:1699.
[7] Calder PC, Albers R, Antoine JM, Blum S, Bourdet-Sicard R, Ferns GA, et al. Inflammatory disease processes and interactions with nutrition. Br J Nutr 2009;101(Suppl 1):S1–45.
[8] Calder PC, Bosco N, Bourdet-Sicard R, Capuron L, Delzenne N, Dore J, et al. Health relevance of the modification of low grade inflammation in ageing (inflammageing) and the role of nutrition. Ageing Res Rev 2017;40:95–119.
[9] Calder PC, Ahluwalia N, Brouns F, Buetler T, Clement K, Cunningham K, et al. Dietary factors and low-grade inflammation in relation to overweight and obesity. Br J Nutr 2011;106(Suppl 3):S5–78.
[10] Jafarnejad S, Boccardi V, Hosseini B, Taghizadeh M, Hamedifard Z. A meta-analysis of randomized control trials: the impact of vitamin C supplementation on serum CRP and serum hs-CRP concentrations. Curr Pharmaceut Des 2018;24:3520–8.
[11] Asbaghi O, Sadeghian M, Nazarian B, Sarreshtedari M, Mozaffari-Khosravi H, Maleki V, et al. The effect of vitamin E supplementation on selected inflammatory biomarkers in adults: a systematic review and meta-analysis of randomized clinical trials. Sci Rep 2020;10:17234.
[12] Saboori S, Shab-Bidar S, Speakman JR, Yousefi Rad E, Djafarian K. Effect of vitamin E supplementation on serum C-reactive protein level: a meta-analysis of randomized controlled trials. Eur J Clin Nutr 2015;69:867–73.
[13] Safabakhsh M, Emami MR, Zeinali Khosroshahi M, Asbaghi O, Khodayari S, Khorshidi M, et al. Vitamin C supplementation and C-reactive protein levels: findings from a systematic review and meta-analysis of clinical trials. J Compl Integr Med 2020. https://doi.org/10.1515/jcim-2019-015.
[14] Nappo F, Esposito K, Cioffi M, Giugliano G, Molinari AM, Paolisso G, et al. Postprandial endothelial activation in healthy subjects and in type 2 diabetic patients: role of fat and carbohydrate meals. J Am Coll Cardiol 2002;39:1145–50.
[15] Gombart AF, Pierre A, Maggini S. A review of micronutrients and the immune system-working in harmony to reduce the risk of infection. Nutrients 2020;12:236.
[16] Stevens GA, Beal T, Mbuya MNN, Luo H, Neufeld LM, Global Micronutrient Deficiencies Research Group. Micronutrient deficiencies among preschool-aged children and women of reproductive age worldwide: a pooled analysis of individual-level data from population-representative surveys. Lancet Global Health 2022;10:e1590–9.
[17] Abioye AI, Bromage S, Fawzi W. Effect of micronutrient supplements on influenza and other respiratory tract infections among adults: a systematic review and meta-analysis. BMJ Glob Health 2021;6.
[18] Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients 2020;12:1181.
[19] Beck MA, Nelson HK, Shi Q, Van Dael P, Schiffrin EJ, Blum S, et al. Selenium deficiency increases the pathology of an influenza virus infection. Faseb J 2001;15:1481–3.
[20] Campa A, Baum MK, Bussmann H, Martinez SS, Farahani M, van Widenfelt E, et al. The effect of micronutrient supplementation on active TB incidence early in HIV infection in Botswana. Nutr Diet Suppl 2017;2017:37–45.
[21] Berger MM, Eggimann P, Heyland DK, Chioléro RL, Revelly JP, Day A, et al. Reduction of nosocomial pneumonia after major burns by trace element supplementation: aggregation of two randomised trials. Crit Care 2006;10:R153.
[22] Hemila H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2013:CD000980.
[23] Hemila H. Zinc lozenges and the common cold: a meta-analysis comparing zinc acetate and zinc gluconate, and the role of zinc dosage. JRSM Open 2017;8:2054270417694291.
[24] Florez ID, Veroniki AA, Al Khalifah R, Yepes-Nunez JJ, Sierra JM, Vernooij RWM, et al. Comparative effectiveness and safety of interventions for acute diarrhea and gastroenteritis in children: a systematic review and network meta-analysis. PLoS One 2018;13:e0207701.
[25] Dissanayake HA, de Silva NL, Sumanatilleke M, de Silva SDN, Gamage KKK, Dematapitiya C, et al. Prognostic and therapeutic role of vitamin D in COVID-19: systematic review and meta-analysis. J Clin Endocrinol Metab 2022;107:1484–502.
[26] Beran A, Mhanna M, Srour O, Ayesh H, Stewart JM, Hjouj M, et al. Clinical significance of micronutrient supplements in patients with coronavirus disease 2019: a comprehensive systematic review and meta-analysis. Clin Nutr ESPEN 2022;48:167–77.
[27] Stoffel NU, Uyoga MA, Mutuku FM, Frost JN, Mwasi E, Paganini D, et al. Iron deficiency anemia at time of vaccination predicts decreased vaccine response and iron supplementation at time of vaccination increases humoral vaccine response: a birth cohort study and a randomized trial follow-up study in Kenyan infants. Front Immunol 2020;11:1313.
[28] Frost JN, Tan TK, Abbas M, Wideman SK, Bonadonna M, Stoffel NU, et al. Hepcidin-mediated hypoferremia disrupts immune responses to vaccination and infection. Méd 2021;2:164–179 e12.
[29] Claessens M, Contor L, Dhonukshe-Rutten R, De Groot LC, Fairweather-Tait SJ, Gurinovic M, et al. EURRECA-Principles and future for deriving micronutrient recommendations. Crit Rev Food Sci Nutr 2013;53:1135–46.
[30] Yetley EA, MacFarlane AJ, Greene-Finestone LS, Garza C, Ard JD, Atkinson SA, et al. Options for basing Dietary Reference Intakes (DRIs) on chronic disease endpoints: report from a joint US-/Canadian-sponsored working group. Am J Clin Nutr 2017;105:249S–85S.
[31] Network Iodine Global, (IGN). Global scorecard of iodine nutrition in 2021 in the general population based on school-age children. 2021. https://ignorg/app/uploads/2023/04/IGN_Global_Scorecard_2021_7_May_2021pdf.
[32] Cohen-Solal A, Philip JL, Picard F, Delarche N, Taldir G, Gzara H, et al. Iron deficiency in heart failure patients: the French CARENFER prospective study. ESC Heart Fail 2022;9:874–84.
[33] Hwa YL, Rashtak S, Kelly DG, Murray JA. Iron deficiency in long-term parenteral nutrition therapy. J Parenter Enteral Nutr 2016;40:869–76.
[34] Ironman Investigators, Litton E, Baker S, Erber WN, Farmer S, Ferrier J, et al. Intravenous iron or placebo for anaemia in intensive care: the IRONMAN multicentre randomized blinded trial : a randomized trial of IV iron in critical illness. Intensive Care Med 2016;42:1715–22.
[35] Lasocki S, Asfar P, Jaber S, Ferrandiere M, Kerforne T, Asehnoune K, et al. Impact of treating iron deficiency, diagnosed according to hepcidin quantification, on outcomes after a prolonged ICU stay compared to standard care: a multicenter, randomized, single-blinded trial. Crit Care 2021;25:62.
[36] Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med 2009;35:1728–37.
[37] Parliament European, Council. Commission delegated regulation (EU) 2016/128 supplementing Regulation (EU) No 609/2013 for food for special medical purposes. Off J EU 2016;25:30–42.
[38] Iacone R, Scanzano C, Santarpia L, D'Isanto A, Contaldo F, Pasanisi F. Micronutrient content in enteral nutrition formulas: comparison with the dietary reference values for healthy populations. Nutr J 2016;15:30.
[39] Blaauw R, Osland E, Sriram K, Ali A, Allard JP, Ball P, et al. Parenteral provision of micronutrients to adult patients: an expert consensus paper. J Parenter Enteral Nutr 2019;43(Suppl 1):S5–23.
[40] Plogsted S, Adams SC, Allen K, Cober MP, Greaves J, Mogensen KM, et al. Parenteral nutrition multivitamin product shortage considerations. Nutr Clin Pract 2016;31:556–9.
[41] Plogsted S, Adams SC, Allen K, Cober MP, Greaves J, Mogensen KM, et al. Parenteral nutrition trace element product shortage considerations. Nutr Clin Pract 2016;31:843–7.
[42] Farrer K, Harrison S, Baker M, Batra A, Cooper SC, Culkin A, et al. Advice during a shortage of intravenous micronutrients for patients receiving parenteral nutrition. Brit Intes Fail All (BIFA) Pos Stat 2021:2022. https://www.bapen.org.uk/pdfs/bifa/position-statements/advice-during-a-shortage-of-iv-micronutrients-for-patients-receiving-pn-updated-08-11-21.pdf.
[43] Joly F, Mundi M, Barazzoni R, Berger MM, Bozzetti F, Cuerda C, et al. How to deal with micronutrient product shortage - editorial. Clin Nutr 2023;42:143–7.
[44] Greenlee H, Kwan ML, Ergas IJ, Strizich G, Roh JM, Wilson AT, et al. Changes in vitamin and mineral supplement use after breast cancer diagnosis in the Pathways Study: a prospective cohort study. BMC Cancer 2014;14:382.
[45] Ambrosone CB, Zirpoli GR, Hutson AD, McCann WE, McCann SE, Barlow WE, et al. Dietary supplement use during chemotherapy and survival outcomes of patients with breast cancer enrolled in a cooperative group clinical trial (SWOG S0221). J Clin Oncol 2020;38:804–14.
[46] Greenlee H, Neugut AI, Falci L, Hillyer GC, Buono D, Mandelblatt JS, et al. Association between complementary and alternative medicine use and breast cancer chemotherapy initiation: the breast cancer quality of care (BQUAL) study. JAMA Oncol 2016;2:1170–6.
[47] Luchtel RA, Bhagat T, Pradhan K, Jacobs Jr WR, Levine M, Verma A, et al. High-dose ascorbic acid synergizes with anti-PD1 in a lymphoma mouse model. Proc Natl Acad Sci U S A 2020;117:1666–77.
[48] Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA A Cancer J Clin 2012;62:243–74.
[49] Prado CM, Purcell SA, Laviano A. Nutrition interventions to treat low muscle mass in cancer. J Cachexia Sarcopenia Muscle 2020;11:366–80.
[50] Gröber U, Holzhauer P, Kisters K, Holick MF, Adamietz IA. Micronutrients in oncological intervention. Nutrients 2016;8:163.
[51] Spencer AS, da Silva Dias D, Capelas ML, Pimentel F, Santos T, Neves PM, et al. Managing severe dysgeusia and dysosmia in lung cancer patients: a systematic scoping review. Front Oncol 2021;11:774081.
[52] Schmidt SF, Rohm M, Herzig S, Berriel Diaz M. Cancer cachexia: more than skeletal muscle wasting. Trends Cancer 2018;4:849–60.
[53] Argiles JM, Lopez-Soriano FJ, Stemmler B, Busquets S. Cancer-associated cachexia - understanding the tumour macroenvironment and microenvironment to improve management. Nat Rev Clin Oncol 2023;20:250–64.

[54] Bindels LB, Neyrinck AM, Claus SP, Le Roy CI, Grangette C, Pot B, et al. Synbiotic approach restores intestinal homeostasis and prolongs survival in leukaemic mice with cachexia. ISME J 2016;10:1456–70.
[55] Johal J, Han CY, Joseph R, Munn Z, Agbejule OA, Crawford-Williams F, et al. Dietary supplements in people with metastatic cancer who are experiencing malnutrition, cachexia, sarcopenia, and frailty: a scoping review. Nutrients 2022;14:2642.
[56] Dev R, Del Fabbro E, Schwartz GG, Hui D, Palla SL, Gutierrez N, et al. Preliminary report: vitamin D deficiency in advanced cancer patients with symptoms of fatigue or anorexia. Oncol 2011;16:1637–41.
[57] Zeichner SB, Koru-Sengul T, Shah N, Liu Q, Markward NJ, Montero AJ, et al. Improved clinical outcomes associated with vitamin D supplementation during adjuvant chemotherapy in patients with HER2+ nonmetastatic breast cancer. Clin Breast Cancer 2015;15:e1–11.
[58] Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr 2016;35:247–307.
[59] Abdalian R, Fernandes G, Duerksen D, Jeejeebhoy KN, Whittaker S, Gramlich L, et al. Prescription of trace elements in adults on home parenteral nutrition: current practice based on the Canadian Home Parenteral Nutrition Registry. J Parenter Enteral Nutr 2013;37:410–5.
[60] ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. J Parenter Enteral Nutr 2002;26(1):1SA–138SA.
[61] Btaiche IF, Carver PL, Welch KB. Dosing and monitoring of trace elements in long-term home parenteral nutrition patients. J Parenter Enteral Nutr 2011;35:736–47.
[62] Uzzan M, Kirchgesner J, Poupon J, Corcos O, Pingenot I, Joly F. Antioxidant trace elements serum levels in long-term parenteral nutrition (PN): prevalence and infectious risk associated with deficiencies, a retrospective study from a tertiary home-PN center. Clin Nutr 2017;36:812–7.
[63] Zafirovska M, Zafirovski A, Rotovnik Kozjek N. Current insights regarding intestinal failure-associated liver disease (IFALD): a narrative review. Nutrients 2023;15.
[64] Voland L, Le Roy T, Debedat J, Clement K. Gut microbiota and vitamin status in persons with obesity: a key interplay. Obes Rev 2022;23:e13377.
[65] Magnusdottir S, Ravcheev D, de Crecy-Lagard V, Thiele I. Systematic genome assessment of B-vitamin biosynthesis suggests co-operation among gut microbes. Front Genet 2015;6:148.
[66] Hossain KS, Amarasena S, Mayengbam S. B vitamins and their roles in gut health. Microorganisms 2022;10.
[67] Belda E, Voland L, Tremaroli V, Falony G, Adriouch S, Assmann KE, et al. Impairment of gut microbial biotin metabolism and host biotin status in severe obesity: effect of biotin and prebiotic supplementation on improved metabolism. Gut 2022;71:2463–80.
[68] Yao Y, Zhu L, He L, Duan Y, Liang W, Nie Z, et al. A meta-analysis of the relationship between vitamin D deficiency and obesity. Int J Clin Exp Med 2015;8:14977–84.
[69] Astrup A, Bugel S. Overfed but undernourished: recognizing nutritional inadequacies/deficiencies in patients with overweight or obesity. Int J Obes 2019;43:219–32.
[70] Goncalves TJM, Seab Goncalves, Guarnieri A, Risegato RC, Guimaraes MP, de Freitas DC, et al. Prevalence of obesity and hypovitaminosis D in elderly with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Nutr ESPEN 2020;40:110–4.
[71] Sadat-Ali M, AlTabash KW, Al-Turki HA, AlMousa SA, AlSayed HN. Time out: should vitamin D dosing be based on patient's body mass index (BMI): a prospective controlled study. J Nutr Sci 2021;10:e106.
[72] Smelt HJM, Pouwels S, Smulders JF, Hazebroek EJ. Patient adherence to multivitamin supplementation after bariatric surgery: a narrative review. J Nutr Sci 2020;9:e46.
[73] Goodman JC. Neurological complications of bariatric surgery. Curr Neurol Neurosci Rep 2015;15:79.
[74] Griffith DP, Liff DA, Ziegler TR, Esper GJ, Winton EF. Acquired copper deficiency: a potentially serious and preventable complication following gastric bypass surgery. Obesity 2009;17:827–31.
[75] Alamri SH, Abdeen GN. Maternal nutritional status and pregnancy outcomes post-bariatric surgery. Obes Surg 2022;32:1325–40.
[76] Bretón I, Ballesteros-Pomar MD, Calle-Pascual A, Alvarez-Sala LA, Rubio-Herrera MA. Micronutrients in pregnancy after bariatric surgery: a narrative review. Preprint. 2023. p. 2023061369. https://doi.org/10.20944/preprints202306.1369.v1.
[77] Falcone V, Stopp T, Feichtinger M, Kiss H, Eppel W, Husslein PW, et al. Pregnancy after bariatric surgery: a narrative literature review and discussion of impact on pregnancy management and outcome. BMC Pregnancy Childbirth 2018;18:507.
[78] Spoelstra–de Man AME, Oudemans–van Straaten HM, Berger MM. Adjuvant vitamin C for sepsis: mono or triple? Crit Care 2019;23:425.
[79] Spoelstra-de Man AME, Oudemans-van Straaten HM, Elbers PWG. Vitamin C and thiamine in critical illness. BJA Educ 2019;19:290–6.
[80] Lamontagne F, Masse MH, Menard J, Sprague S, Pinto R, Heyland DK, et al. Intravenous vitamin C in adults with sepsis in the intensive care unit (LOVIT). N Engl J Med 2022;386:2387–98.
[81] Liang B, Su J, Shao H, Chen H, Xie B. The outcome of IV vitamin C therapy in patients with sepsis or septic shock: a meta-analysis of randomized controlled trials. Crit Care 2023;27:109.
[82] Cherukuri L, Gewirtz G, Osea K, Tayek JA. Vitamin A treatment for severe sepsis in humans; a prospective randomized double blind placebo-controlled clinical trial. Clin Nutr ESPEN 2019;29:49–51.
[83] Chen J. An original discovery: selenium deficiency and Keshan disease (an endemic heart disease). Asia Pac J Clin Nutr 2012;21:320–6.
[84] Benstoem C, Goetzenich A, Kraemer S, Borosch S, Manzanares W, Hardy G, et al. Selenium and its supplementation in cardiovascular disease–what do we know? Nutrients 2015;7:3094–118.
[85] Rayman MP. Selenium and human health. Lancet 2012;379:1256–68.
[86] Manzanares W, Dhaliwal R, Jiang X, Murch L, Heyland DK. Antioxidant micronutrients in the critically ill: a systematic review and meta-analysis. Crit Care 2012;16:R66.
[87] Bloos F, Trips E, Nierhaus A, Briegel J, Heyland DK, Jaschinski U, et al. Effect of sodium selenite administration and procalcitonin-guided therapy on mortality in patients with severe sepsis or septic shock: a randomized clinical trial. JAMA Intern Med 2016;176:1266–76.
[88] Heyland DK, Dhaliwal R. Role of Glutamine supplementation in critical illness given the results of the REDOXS study. J Parenter Enteral Nutr 2013;37:442–3.
[89] Mousavi MA, Saghaleini SH, Mahmoodpoor A, Ghojazadeh M, Mousavi SN. Daily parenteral selenium therapy in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Clin Nutr ESPEN 2021;41:49–58.
[90] Kurmis R, Greenwood J, Aromataris E. Trace element supplementation following severe burn injury: a systematic review and meta-analysis. J Burn Care Res 2016;37:143–59.
[91] Amrein K, Venkatesh B. Vitamin D and the critically ill patient. Curr Opin Clin Nutr Metab Care 2012;15:188–93.
[92] Amrein K, Oudemans-van Straaten HM, Berger MM. Vitamin therapy in critically ill patients: focus on thiamine, vitamin C, and vitamin D. Intensive Care Med 2018;44:1940–4.
[93] Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev 2014:CD007470.
[94] Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ 2017;356:i6583.
[95] Pittas AG, Kawahara T, Jorde R, Dawson-Hughes B, Vickery EM, Angellotti E, et al. Vitamin D and risk for type 2 diabetes in people with prediabetes : a systematic review and meta-analysis of individual participant data from 3 randomized clinical trials. Ann Intern Med 2023;176:355–63.
[96] Crowe FL, Mughal MZ, Maroof Z, Berry J, Kaleem M, Abburu S, et al. Vitamin D for growth and rickets in stunted children: a randomized trial. Pediatrics 2021;147:e20200815.
[97] Griffin G, Hewison M, Hopkin J, Kenny RA, Quinton R, Rhodes J, et al. Perspective: vitamin D supplementation prevents rickets and acute respiratory infections when given as daily maintenance but not as intermittent bolus: implications for COVID-19. Clin Med 2021;21:e144–9.
[98] Menger J, Lee ZY, Notz Q, Wallqvist J, Hasan MS, Elke G, et al. Administration of vitamin D and its metabolites in critically ill adult patients: an updated systematic review with meta-analysis of randomized controlled trials. Crit Care 2022;26:268.
[99] Amrein K, Parekh D, Westphal S, Preiser JC, Berghold A, Riedl R, et al. Effect of high-dose vitamin D3 on 28-day mortality in adult critically ill patients with severe vitamin D deficiency: a study protocol of a multicentre, placebo-controlled double-blind phase III RCT (the VITDALIZE study). BMJ Open 2019;9:e031083.
[100] Koekkoek WAC, Van Zanten ARH. Is refeeding syndrome relevant for critically ill patients? Curr Opin Clin Nutr Metab Care 2018;21:130–7.
[101] Olthof LE, Koekkoek WACK, van Setten C, Kars JCN, van Blokland D, van Zanten ARH. Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: a retrospective study. Clin Nutr 2018;37:1609–17.
[102] Doig GS, Simpson F, Heighes PT, Bellomo R, Chesher D, Caterson ID, et al. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med 2015;3:943–52.
[103] Singer P, Reintam-Blaser A, Berger MM, Alhazzani W, Calder PC, Casaer M, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38:48–79.
[104] Deane AM, Jiang A, Tascone B, Clancy A, Finnis ME, Collie JT, et al. A multicenter randomized clinical trial of pharmacological vitamin B1 administration to critically ill patients who develop hypophosphatemia during enteral nutrition (The THIAMINE 4 HYPOPHOSPHATEMIA trial). Clin Nutr 2021;40:5047–52.
[105] Thomas DT, Erdman KA, Burke LM. Position of the academy of nutrition and dietetics, dietitians of Canada, and the American college of sports medicine: nutrition and athletic performance. J Acad Nutr Diet 2016;116:501–28.
[106] Burden RJ, Morton K, Richards T, Whyte GP, Pedlar CR. Is iron treatment beneficial in, iron-deficient but non-anaemic (IDNA) endurance athletes? A systematic review and meta-analysis. Br J Sports Med 2015;49:1389–97.
[107] Zhang L, Quan M, Cao ZB. Effect of vitamin D supplementation on upper and lower limb muscle strength and muscle power in athletes: a meta-analysis. PLoS One 2019;14:e0215826.

[108] Draeger CL, Naves A, Marques N, Baptistella AB, Carnauba RA, Paschoal V, et al. Controversies of antioxidant vitamins supplementation in exercise: ergogenic or ergolytic effects in humans? J Int Soc Sports Nutr 2014;11:4.
[109] Sayer AA, Syddall H, Martin H, Patel H, Baylis D, Cooper C. The developmental origins of sarcopenia. J Nutr Health Aging 2008;12:427–32.
[110] Hanach NI, McCullough F, Avery A. The impact of dairy protein intake on muscle mass, muscle strength, and physical performance in middle-aged to older adults with or without existing sarcopenia: a systematic review and meta-analysis. Adv Nutr 2019;10:59–69.
[111] Buondonno I, Sassi F, Carignano G, Dutto F, Ferreri C, Pili FG, et al. From mitochondria to healthy aging: the role of branched-chain amino acids treatment: MATeR a randomized study. Clin Nutr 2020;39:2080–91.
[112] Sahni S, Dufour AB, Fielding RA, Newman AB, Kiel DP, Hannan MT, et al. Total carotenoid intake is associated with reduced loss of grip strength and gait speed over time in adults: the Framingham Offspring Study. Am J Clin Nutr 2021;113:437–45.
[113] De Spiegeleer A, Beckwee D, Bautmans I, Petrovic M. Sarcopenia guidelines development group of the Belgian society of gerontology, geriatrics. Pharmacological interventions to improve muscle mass, muscle strength and physical performance in older people: an umbrella review of systematic reviews and meta-analyses. Drugs Aging 2018;35:719–34.
[114] Garcia-Casares N, Gallego Fuentes P, Barbancho MA, Lopez-Gigosos R, Garcia-Rodriguez A, Gutierrez-Bedmar M. Alzheimer's disease, mild cognitive impairment and mediterranean diet. A systematic review and dose-response meta-analysis. J Clin Med 2021;10.
[115] Staubo SC, Aakre JA, Vemuri P, Syrjanen JA, Mielke MM, Geda YE, et al. Mediterranean diet, micronutrients and macronutrients, and MRI measures of cortical thickness. Alzheimers Dement 2017;13:168–77.
[116] Fostinelli S, Ferrari C, De Amicis R, Giustizieri V, Leone A, Bertoli S, et al. The impact of nutrition on cognitive performance in a frail elderly population living in northern Italy. J Am Nutraceutical Assoc 2023;42:484–94.